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Pd(II)-Catalyzed *ortho*-C−H Oxidation of Arylacetic Acid Derivatives: Synthesis of Benzofuranones

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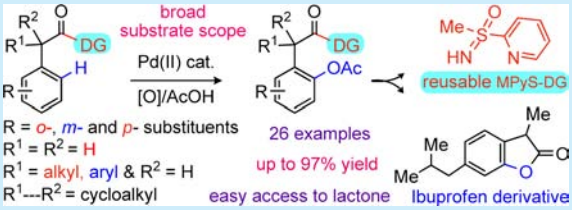
Supporting Information

ABSTRACT: Pd(II)-catalyzed *ortho*-C−H acetoxylation of arylacetic acid derivatives is demonstrated with the aid of a novel *S*-methyl-*S*-2-pyridylsulfoximine (MPyS) directing group (DG). The *α*-mono- and *α*-unsubstituted arylacetic acid derivatives were readily employed in the *ortho*-C−H acetoxylations. The oxidation products are hydrolyzed, and the MPyS-DG is easily recovered, providing ready access to *o*-hydroxyarylacetic acids. 3-Mono- and 3-unsubstituted benzofuranones are synthesized from *o*-hydroxyarylacetic acids.

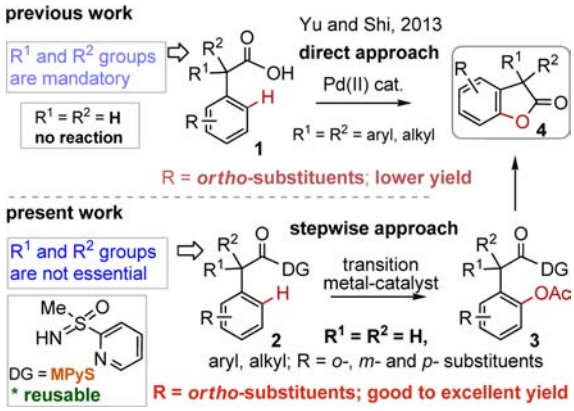


Transition-metal-catalyzed C−H bond functionalization has emerged as a useful, step-economical method for the direct conversion of C−H bonds proximal to the directing group, to C−C and C−heteroatom bonds with high regioselectivity.[1] Of note, the oxidation of aryl-C(sp^2)−H to aryl-C(sp^2)−O bonds allows the synthesis of structurally diverse and pharmaceutically important phenol derivatives from readily accessible starting materials.[2,3] Due to the broad utility of phenol derivatives, the development of effective strategies for the C(sp^2)−H oxidations is desirable.[4] Aryl carboxylic acids and their derivatives efficiently assist in creating aryl-C(sp^2)−O bonds; in contrast, the oxidation of *o*-C(aryl)−H bond on arylacetic acid through C−H activation is less explored.[3h]

Benzofuranone is an important skeleton widely present in various natural products and biologically active molecules.[5] The following methods, including (I) condensations of 2-(2-hydroxyphenyl)acetic acid,[6a−c] (II) tandem Friedel−Crafts/condensations of phenol with *α*-hydroxy acid,[6d] (III) oxidation of boronic acids and their derivatives,[7] and (IV) transition-metal-catalyzed coupling reactions of phenol derivatives,[8] have successfully been employed, accessing the benzofuranone skeletons. Recently, the Yu[9a] and Shi[9b] groups have independently developed Pd(II)-catalyzed direct cyclization of arylacetic acids for the synthesis of 3,3-disubstituted benzofuranones (Scheme 1). On the basis of the Thorpe−Ingold effect, the *α*,*α*′-disubstituted arylacetic acids exclusively participated in the cyclization by activating the *ortho*-aryl-C−H bond (Scheme 1). However, the application of these methodologies to the synthesis of 3-mono- and 3-unsubstituted benzofuranones has thus far been unsuccessful.[9] Furthermore, the *para*- and *meta*-substituted arylacetic acids underwent cyclizations efficiently, whereas the *ortho*-substituted arylacetic acids reacted sluggishly, delivering poor yield of the benzofuranones (Scheme 1).[9]

Our recent accomplishments on the methylphenylsulfoximine (MPS) and methyl-2-pyridylsulfoximine (MPyS) reusable DG-assisted aryl-C(sp^2)−O and primary *β*−C(sp^3)−O

Scheme 1. Synthesis of Benzofuranones via Metal-Catalyzed *ortho*-C−H Activation of Arylacetic Acid Derivatives



bond formations inspired us to envisage the synthesis of structurally diverse benzofuranone from arylacetic acid derivatives following the acetoxylation of the aryl-C(sp^2)−H bond and lactonization sequence (Scheme 1).[10] Furthermore, we intend to achieve the oxidation of the aryl-C(sp^2)−H bond of *ortho*-substituted and *α*-unsubstituted arylacetic acids (Scheme 1). Herein we demonstrated the Pd(II)-catalyzed MPyS-DG-assisted *ortho*-C−H acetoxylation of arylacetic acid derivatives and the synthesis of 3-unsubstituted benzofuranones.

A wide array of phenylacetic acid derivatives having mono- and bidentate DGs were synthesized and subjected to the known *ortho*-aryl-C−H oxidation conditions comprising Pd(OAc)$_2$ (10 mol %) and $K_2S_2O_8$ (1.5 equiv) in AcOH at 50 °C (Scheme 2).[11] The monodentate directing groups −NHOMe and −NHC$_6$H$_4$-4-NO$_2$ on phenylacetic acid (**1a**) did not oxidize the *ortho*-aryl-C−H bond; surprisingly, the −NHC$_6$F$_5$

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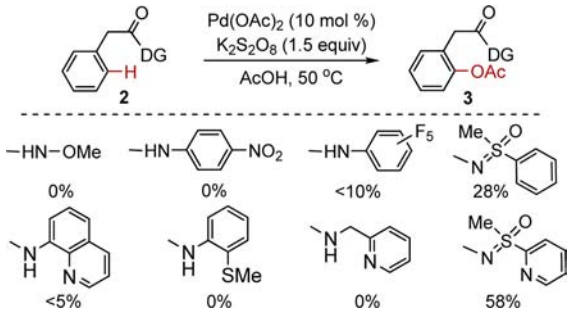
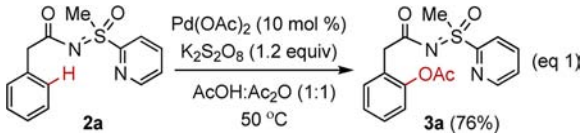
Scheme 2. Screening of Different Directing Groups



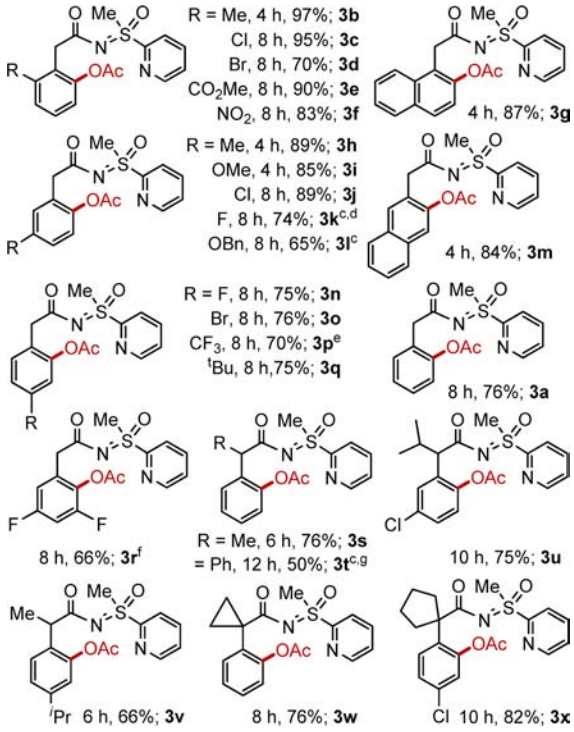
and MPS DGs allowed formation of the desired *ortho*-C−H acetoxylation products in <10 and 28% yields, respectively (Scheme 2).[11]

To our disappointment, the bidentate DGs 8-amino quinoline, 2-thiomethyl aniline, and 2-picolyl amine attached phenylacetic acid derivatives failed to yield the corresponding *ortho*-aryl-C−H oxidation products. To our delight, the recently developed MPyS-DG assists introducing an acetoxy group at the *ortho*-aryl-C−H bond in phenylacetic acid moiety, delivering the desired *N*-[2-(2-acetoxyphenyl)acetyl]-*S*-methyl-*S*-2-pyridylsulfoximine (**3a**) in 58% yield. Further screening of the catalysts, oxidants, and solvents led to the finer optimized conditions [**2a** (1.0 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), $K_2S_2O_8$ (1.2 equiv) in 1:1 mixture of AcOH and Ac_2O at 50 °C], producing **3a** in 76% isolated yield (eq 1).[11]



The optimized conditions shown in eq 1 were explored by examining the scope and generality of the *o*-C−H acetoxylations on compounds **2a−x**, and the results are summarized in Scheme 3. The lower yield encountered in the C−H oxidation of *ortho*-substituted arylacetic acids[9] provoked us to investigate the *ortho*-C−H acetoxylation of MPyS-DG containing arylacetic acid derivatives (**2b−f**), at first. Gratifyingly, the acetoxylated product **3b** was isolated in 97% yield from electron-rich 2-*o*-tolylacetic acid derivative **2b**. The synthetically important chloro- and bromo-group-substituted **2c** and **2d** underwent acetoxylation smoothly to produce **3c** and **3d** in 95 and 70% yields, respectively. Strong electron-withdrawing groups CO_2Me (**2e**) and NO_2 (**2f**) on the aryl ring surprisingly did not affect the reaction outcome, and the desired acetoxylation products were isolated in excellent yields. The α-naphthyl derivative **2g** gave 87% of **3g**. The regioselectivity in the C−H acetoxylation was evaluated by submitting the *meta*-substituted arylacetic acid derivatives to the optimized conditions. A highly regioselective *ortho*-acetoxylation occurred on the sterically less hindered side of the aryl ring in *m*-Me (**2h**), *m*-OMe (**2i**), *m*-Cl (**2j**), and *m*-F (**2k**) substituted arylacetic acids; the corresponding products were isolated in high yields [**3h** (89%), **3i** (85%), **3j** (89%), and **3k** (74%)].[11] The *m*-O-benzyl group on the aryl ring did not affect the reaction; the acetoxy group was inserted at the less hindered side, producing **3l** in moderate yield. Similarly, the 2-(β-naphthyl)acetic acid derivative **2m** gave the desired acetoxylated product **3m** in 84% yield. The *ortho*-acetoxylated products

Scheme 3. Acetoxylation of Arylacetic Acid Derivatives[a,b]



[a]Reaction conditions: **2** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), $K_2S_2O_8$ (0.6 mmol), AcOH/Ac_2O (3.0 mL, 1:1) at 50 °C. [b]Isolated yields. [c]Reaction was conducted using 0.25 mmol of **2**. [d]A trace amount (<5%) of sterically hindered *o*-C-2-acetoxylation product was formed. [e]Reaction was conducted with 0.3 mmol of **2p**. [f]Heated at 80 °C. [g]AcOH was used as solvent.

3n−q and **3a** were successfully obtained in good yields from the *para*-substituted and electron-neutral phenylacetic acid derivatives **2n−q** and **2a**, respectively. The sterically hindered 2-(3,5-difluorophenyl)acetic acid derivative **2r** led to 66% of **3r**.

The effect of the α-substituent on arylacetic acid derivative toward the *o*-C−H acetoxylations was studied next. The acetoxylation of α-methyl (**2s**), α-phenyl (**2t**), and α-*iso*-propyl (**2u**) substituted compounds occurred smoothly to produce **3s**, **3t**, and **3u** in moderate to good yields.[12] Ibuprofen is an anti-inflammatory drug;[13] the MPyS bearing ibuprofen **2v** is acetoxylated to afford **3v** in good yield. The α,α'-disubstituted cyclopropyl (**2w**)[12] and cyclopentyl (**2x**) compounds were independently reacted under the optimized conditions, giving 76 and 82% of **3w** and **3x**, respectively.

The synthetic utility of this method is demonstrated with the hydrolysis of the acetoxylation products; this would lead to the *o*-hydroxyarylacetic acids, a precursor to benzofuranones, and the recovery of the MPyS DG (Table 1).[10,14] Hydrolysis of the acetoxylated products **3** with 2 N HCl occurred smoothly. Accordingly, the *o*-hydroxyarylacetic acids **4′a−d** were prepared from the hydrolysis of **3a**, **3f**, **3m**, and **3v**, respectively. Subsequently, lactonizations of **4′a−d** in the presence of $POCl_3$ in $ClCH_2CH_2Cl$ delivered 3,3-unsubstituted benzofuranones **4a−c** and ibuprofen derivative **4d** in overall good isolated yields (entries 1−4, Table 1).

We next performed the *o*-acyloxylation of **2b** using different carboxylic acid solvent. The carboxylate group $CD_3COO−$ or $EtCOO−$ was smoothly incorporated by replacing the *o*-C−H bond leading to **5a** (82%) and **5b** (76%) (Scheme 4). The acid

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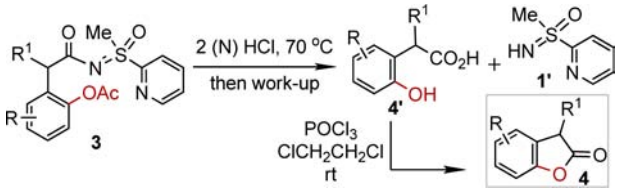
Table 1. Removal of MPyS-DG and Lactonization[a]

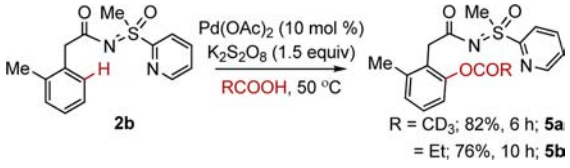


entry	3	t (h)	yield of 4[b]	yield of MPyS[c]
1	3a	12	4a, 78%	89
2	3f	15	4b, 82%	84
3	3m	15	4c, 78%	83
4	3v	15	4d, 82%	87

[a]Reaction conditions: (i) **3** (0.25 mmol), 3.0 mL of 2 N HCl at 70 °C; (ii) $POCl_3$ (5.0 equiv). [b]Isolated yield of benzofuranones (**4**) over two steps. [c]Isolated yields of MPyS.

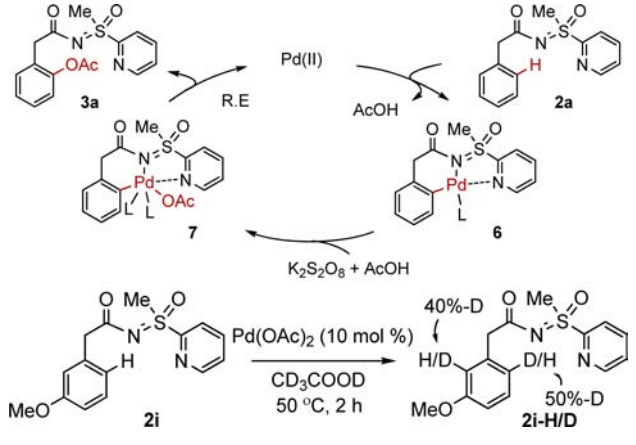
solvent presumably serves as the source of oxygen for the C−O bond formation.

Scheme 4. Acyloxylation of Arylacetic Acid Derivative



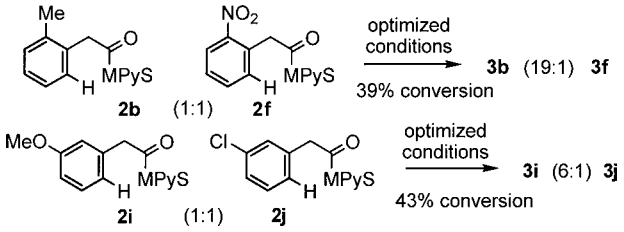
Based on the preliminary mechanistic study and previous reports, a plausible mechanistic cycle is proposed in Scheme 5. The activation of the *ortho*-C−H bond of **2a** by the Pd(II) catalyst through concerted metalation deprotonation (CMD) leads to cyclometalated species **6**. A controlled H/D scrambling study reveals the reversible nature of C−H activation under the present catalytic cycle (**2i-H/D**).[11,15] The oxidation of the Pd(II) species in **6** to Pd(IV) in **7** occurs smoothly with $K_2S_2O_8$ in AcOH.[16] Finally, the reductive elimination of **7** produces the desired acetoxylated product **3a**.

Scheme 5. Plausible Mechanistic Cycle



The competition experiments were performed to study the electronic effect of the substituents on the aryl ring (Scheme 6).

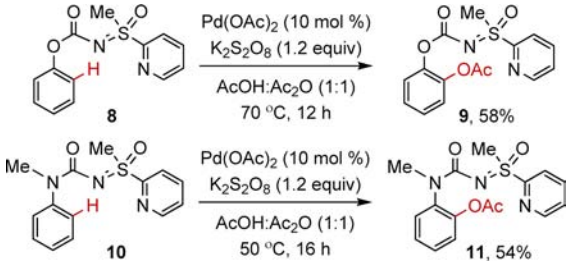
Scheme 6. Competition Experiments



The reaction of an equimolar mixture of **2b** and **2f** under the optimized conditions gave **3b** and **3f** in overall 39% yield in a 19:1 ratio. Similarly, a 6:1 mixture of **3i** and **3j** was observed from **2i** and **2j** in overall 43% yield. It appears that the electron-donating substituents on arenes allow faster reaction over the electron-deficient arenes.

To show the strength of MPyS DG, the acetoxylation of carbamate **8** and urea **10** derivatives was independently conducted under the optimized conditions. The corresponding C−H acetoxylation products **9** and **11** were isolated in moderate yield (Scheme 7).

Scheme 7. Acetoxylation of Carbamate and Urea Derivatives



In conclusion, we have developed a novel MPyS directing group assisted Pd(II)-catalyzed *o*-acetoxylation of arylacetic acid derivatives with broad substrate scope. The oxidation of *o*-substituted arylacetic acids gave excellent yields of the desired *o*-C−H acetoxylation products. The acetoxylated products are successfully hydrolyzed to *o*-hydroxyarylacetic acid, an effective precursor to benzofuranones, and MPyS directing group in good yields. Using this protocol, the 3-mono- and 3-unsubstituted benzofuranones are readily synthesized. Current effort is directed at exploring the synthetic applications of this transformation.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) For more details, see the Supporting Information.

(12) The C(sp^3)−H/N−Me acetoxylation or the cyclopropyl cleaved products are not observed.

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